

Research Paper: The Association of Depressive Symptoms With Plasma C-Reactive Protein in Patients With Major Depressive Disorder Under Treatment



Azher Nema Mohammed Al-Agam¹, Ammar Waheeb Obeiad², Mahir Abdulkadhum Khudhair Alzughaibi², Hayder Abdul-Amir M. Al-Hindy^{3*}, Amer Fadhil Alhaideri⁴

1. Department of Psychiatry, Merjan Teaching Hospital, Babil Health Directorate, Babylon, Iraq.

2. Merjan Teaching Hospital, Babil Health Directorate, Babylon, Iraq.

3. Department of Pharmacology and Toxicology, School of Pharmacy, University of Babylon, Hilla City, Babylon, Iraq.

4. Department of Medicine, School of Medicine, Karbala University, Karbala, Iraq.



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ABSTRACT

Objectives: This study evaluates the relationship between plasma high sensitive c-reactive protein (HSCRP) in patients with Major Depressive Disorder (MDD) under therapy.

Methods: This cross-sectional study included 90 patients with MDD that had been diagnosed previously to confirm their matching «DSM-5 criteria for MDD version 7.0.2,» employing the «mini-international neuropsychiatric interview.» Also, they were on antidepressants prescriptions for at least 4 months. The criteria of MDD were based on the self-administered inquiry forms for evaluating depression severity, comprising the 9-item Patient Health Questionnaire (PHQ-9) depression module. A venous blood sample was collected from all participants for White Blood Cells (WBCs) counts and HSCRP assays. Besides their BMI calculations, SPSS v. 23, was used for all statistical tests.

Results: HSCRP mean serum levels were within normal ranges among MDD patients. The Mean±SD age of the MDD patients was 39.5±0.9 years, and most of them were obese; their Mean±SD BMI was 32.9±15.8 kg/m². The mean WBCs count of the participants was within the normal ranges. The ratio of male/female participants in this study was 1.64:1. There was a non-significant difference between the sexes in all study parameters: no significant variations in the distribution of HSCRP levels according to the scores of depression severity. There was no significant variation in the distribution of WBCs counts according to the severity of depressive thoughts. A receiver operating characteristic curve (when tested for the diagnostic ability of HSCRP) revealed poor predictability to distinguish those with severe MDD from those with no or mild depressive thoughts: area under the curve=0.484, sensitivity=0.52, specificity=0.46, and P>0.05.

Discussion: The outcomes of our study highlighted the importance of low-grade inflammation as a risk factor of the onset or even worsening of depression in patients with MDD. This finding is reflected by a significant difference in the mean levels of serum HSCRP between those having mild and severe PHQ-9 scores. However, the mean serum levels of HSCRP were not correlated with the severity of depressive symptoms.

* Corresponding Author:

Hayder Abdul-Amir M. Al-Hindy, MD.

Address: Department of Pharmacology and Toxicology, School of Pharmacy, University of Babylon, Hilla City, Babylon, Iraq.

Tel: +96 (47) 708020200

E-mail: phar.hayder.abdul@uobabylon.edu.iq

Highlights

- Although MDD is not a pure inflammatory disorder, inflammation vigorously contributes to the severity of depression.
- There is a significant difference in the mean levels of HSCRP between those having mild and those with mild to severe depression based on the 9-item PHQ-9 depression module scores.
- Low-grade inflammation is a significant risk factor for the onset or exacerbation of depression in patients with MDD.
- Further studies should explore the mechanisms involved in the association of inflammation and MDD, which may improve understanding of these conditions and design more targeted therapies.

Plain Language Summary

As a prevailing disorder, depression can result in substantial burdens and debilities worldwide. Of many emerging recent risk factors, inflammation had a documented contribution to several human diseases. C-reactive protein (CRP) is a known biomarker of systemic body inflammation. Our goal in this study was to assess the role of low-grade inflammation in patients with depression. The study revealed that the depressive patients exhibited higher levels of CRP in their blood, though not correlated with the severity of the symptoms. Meanwhile, there is a significant difference between those having mild and those with moderate to severe depressive scores regarding the mean levels of CRP. These findings suggest the significant role of low-grade inflammation in depressive patients that may predict the onset or even aggravation of the depression symptoms. This observation is essential in future studies to develop more targeted therapies that could help patients with depression.

1. Introduction

Major Depressive Disorder (MDD) is a prevailing disorder that leads to substantial burden and debilities worldwide [1]. It may primarily increase death owing to suicide or secondarily by deteriorating prospects of chronic disorders like Coronary Vascular Disease (CVD) [2]. The well-recognized association between symptoms of MDD and CVD has been doubled the risk of evolving ischemic heart disease [3]. Even though the customary risk factors of CVD tend to gather in depressive subjects due to unhealthy living standards (e.g., poor nutrition, absence of exercise), these ill manners do not sufficiently responsible for the influence of depression on CVD. A potential systematic link between MDD and CVD is low-grade inflammation. Based on the available evidence, depression and CVD are mutual illnesses that frequently arise together. The evidence suggests their planned coincidence and the risk factor of depression by its neuroendocrine pathways induces the pathogenesis and evolution of coronary arteriosclerosis and later heart disease [4, 5]. Although MDD lacks a pure inflammatory pathology, inflammation shows a massive contribution [6] that may predict the onset of depression [7].

Alternatively, higher serum levels of High Sensitive C-Reactive Protein (HSCRP) are a biomarker of a low-grade inflammation [8, 9] associated with the occurrence and prognosis of CVD [10-15]. Consequently, both depression and HSCRP are related to CVD events. Nonetheless, the exact mechanism of their association is still unclear. Several epidemiological studies have described a relationship between depressive symptoms and higher HSCRP in the blood [16-18]. Some academics propose a probable psychoneuroimmunology association between negative affection (depression, rage, nervousness, poor welfare), inflammatory biomarkers, and the evolution of cardiovascular events [19]. The study aimed to evaluate the relationship between plasma HSCRP levels with depressive symptoms, in people with MDD under therapy.

2. Materials and Methods

In this cross-sectional study, the patients with MDD were selected by the psychiatrists at Merjan Teaching Hospital, including the author. The study included 90 adults with previously diagnosed MDD. To confirm their matching “DSM-5 criteria for MDD version 7.0.2” , we employed the mini-international neuropsychiatric interview [20]. They were on antidepressants prescriptions for at least 4-months. MDD patients had enrolled from those attending psychiatric consultation clinics of

Table 1. Basal demographic features of the studied participants

Characteristics	CRP	Age	BMI	WBC
Mean	3.1	39.45	32.9	8.2
Median	0.06	37.0	33.0	8.0
Std. Deviation	0.9	15.8	15.1	2.2
Minimum	0.0	12.0	26.0	4.0
Maximum	0.0	82.0	41.0	14.0

CRP: C-Reactive Protein; BMI: Body Mass Index; WBC: White Blood Cell.

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Merjan Teaching Hospital between April and June 2021, throughout their follow-up appointments. The criteria of MDD were based on the self-administered inquiry forms obtainable for evaluating depression severity, comprising the 9-item Patient Health Questionnaire (PHQ-9) depression module [21]. MDD applicants identify the incidence of every thought that arose throughout the previous week (minimum: 1=not at all to maximum: 4=nearly every day), where upper scores represent higher thought incidence. The overall score is the sum of inquiries 1-30 and labels the incidence of thoughts.

The exclusion criteria included any neurological illnesses like epilepsy, injured or degenerative brain illnesses, drug addicts, and steroid users within the past two months. It is well known that MDD must not be established or omitted only based on a PHQ-9 scoring. A score of PHQ-9 ≥ 10 is 88% sensitive and 88% specific for MDD [22]. Based on this module, the depressed subjects were classified into five groups (scores): (0-4) no depression, (5-9) mild, (10-14) moderate depression, (15-20) moderately severe, and (21-27) severe depression. In the end, a decisive diagnosis was made based on how well the subject understood the inquiry form and other related data from the depressive patient [21].

Fresh venous samples from the participants were collected, centrifuged, and stored for further hematological and biochemical assays. The sampling times were matched among all the applicants. Leukocytes counts were measured based on the available classical methods. Measurements of HSCRP were achieved following the company instructions of "Calbiotech® Netherland, using High Sensitivity C-reactive Protein ELISA kit." Participants' body weight, length, and body mass index were accurately measured.

The data were collected, processed, and examined using SPSS v. 23, USA-IBM. Variations in demographic features were assessed using the t-test for continuous

variables and the Chi-square test for categorical variables. The Pearson correlations were applied to examine the associations between the parameters.

3. Results

The applicants' characteristics are available in Table 1. The HSCRP mean serum levels were within the normal range among MDD patients. The Mean \pm SD age of the MDD patients was 39.5 \pm 0.9 years, and most patients were obese; their Mean \pm SD BMI was 32.9 \pm 15.8 kg/m². The mean WBC counts of the participants were within the normal range.

The ratio of a male/female in this study was 1.64:1. There was a non-significant difference between males and females in all study parameters (Table 2). There were no significant differences in the mean concentrations of serum HSCRP according to the types of antidepressants used by patients with MDD (results not shown) (Table 3). Likewise, no significant variations were seen in the distribution of HSCRP levels regarding the severity of depression scores (Table 4). There was no significant variation in the distribution of WBCs counts in terms of severity of depressive thoughts (Table 5).

Figure 1 displays a significant difference in the mean levels of serum HSCRP between those with low and those with high PHQ-9 scores. Those who were severely symptomatic showed higher levels of HSCRP in their sera. Receiver operation characteristics, when tested for the diagnostic ability of HSCRP, revealed poor predictability to distinguish those with severe MDD from those with no or mild depressive thoughts: area under the curve (AUC)=0.484, sensitivity=0.52, specificity=0.46, and $P > 0.05$ (Figure 2).

Table 2. Sex differences of the study parameters in the participants

Characteristics	Sex	Mean	Std. Error Mean	Significance
HSCRP (mg/mL)	F	10.2	1.4	>0.05
	M	7.5	1.3	
Age (y)	F	41.1	2.1	>0.05
	M	36.9	2.7	
BMI (kg/m ²)	F	32.6	0.9	>0.05
	M	32.9	4.4	
WBC (1x10 ³ /μL)	F	8.3	0.4	>0.05
	M	8.1	0.4	

HSCRP: high sensitive C-reactive protein; BMI: Body Mass Index; WBC, white blood cell.

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4. Discussion

The current study explored the associations of inflammatory biomarkers with patients with MDD among the Iraqi people. The research revealed no direct association between depression and inflammation; however, the mean serum levels of HSCRP were significantly higher in depressive patients with higher PHQ-9 scores than those with lower scores. Our finding is hard to rationalize with a growing body of evidence in current years that has proposed a close association between low-grade inflammation, cytokines levels, and MDD. One of the foremost attentions of this field is the contribution of the immune system in mental wellbeing and psychiatric illnesses [6, 7, 23]. The macrophage concept of depression assumes that the secretion of proinflammatory cytokines by triggered macrophages subsidizes the onset or exacerbation of MDD [24]. Furthermore, in the latest large meta-analysis, a wide range of variations in immune response have been defined in depressive patients, such as greater concentrations of tumor necrosis factor-alpha, interleukin (IL)-6, IL-13, IL-18, IL-12, IL-1RA, and sTNFR2, as well as a fall in the cytokine interferon-gamma [25].

On the other hand, a suppressed inflammatory response has also been reported in depressed subjects [26]. Patients with MDD have a more leukocyte count and CD4+/CD8+ratio, besides less natural killer (NK) cell number with weakened T and NK cell activity as described by a previous meta-analysis [26]. There are few studies revealing inconsistent results of immune stimulation and or suppression in MDD. Indeed, both may ensue in the same subject, like suppression of NK and regulatory T-cell action along with monocytes activation [27].

Meanwhile, a recent study published results similar to our findings and revealed that depression is related to inflammation only in individuals with exact characteristics. The researchers concluded that the associations between MDD, inflammatory response, and covariates were probably highly multivariable and multifactorial that deserve further analysis [28]. A recent review has described a bidirectional association between MDD and inflammation [29]. The multicausal association comprises the likelihood of reverse causality, where depression is not a result, instead the reason for greater inflammatory levels. Besides, the authors found that relations between depressive symptoms and inflammatory biomarkers were weakened after adjusting covariate; BMI and gender constantly exhibited strong associations with inflammatory

Table 3. Mean serum HSCRP levels with respect to WBCs, BMI, and age, which was significant only with WBCs

	Correlation	WBCs	BMI	Age
HSCRP (mg/mL)	Pearson Correlation	0.42	0.139	0.11
	Sig. (2-tailed)	0.000	0.19	0.3

HSCRP: High Sensitive C-Reactive Protein; BMI: Body Mass Index; WBC: White Blood Cell.

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Table 4. Distribution of HSCRP levels in terms of the depression severity

Severity of Depression	Number	Mean±SD	P
No depression	0	0	
Mild depression	6	3.0±2.4	
Moderate depression	25	10.3±8.7	>0.05
Moderate-Severe	59	9.2±9.7	
Severe	0	0	

HSCRP: High Sensitive C-Reactive Protein.

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markers [28]. In the same channel, a highly significant rise of CRP levels was not detected among all MDD patients, but only among those with atypical type or suicidal thoughts, as reported by Egyptian scholars recently [30].

In a systematic review and focused meta-analysis on the association between CRP and MDD, a minor association ($r = 0.05$) was found after adjustment of age, gender, body weight, health conditions, and treatments or psychosocial issues. The influence size was extremely attenuated and not significant in surveys of high-quality scoring. Furthermore, the authors define several recommendations for upcoming studies to consider, like sample assortment and analyzing measures, data filtering, and statistical approaches, and control parameters to evaluate [31].

Numerous factors can alter the inflammatory response and confound the levels of CRP in the blood among MDD subjects. The role of gender on HSCRP levels may be more intricate in the perspective of depressive thoughts. Several studies on CRP and MDD have found conflicting results; some reported raised CRP values in men, but not women [32], and other studies revealed the opposite [33]. Medicines, like statins [34], antihypertensive medication [35], non-steroidal anti-inflammatory drugs [36], and even antidepressants [37], are linked with both CRP and MDD. Some substances like alcohol or caffeine consumption and nicotine (smoking) are associated with CRP values dysregulation [38]. The alternative confounding issue is obesity, in which evidence proposes that the association between CRP and BMI is possibly

determined mostly by obesity [39]. Of note, obesity in our study was common. Socioeconomic status has been consistently and inversely associated with serum levels of HSCRP, often independent of demographic, biological, or behavioral issues [31].

Based on the results mentioned above, the theory that MDD is linked with the inflammatory immune system may be an effective target for therapy. Additional works should emphasize the exact pathways involved in the association of inflammation and MDD, which may help us improve our understanding of these conditions and design more targeted therapies.

5. Conclusion

There was a significant difference in the mean levels of serum HSCRP between those having low and those with high PHQ-9 scores. Those who were severely symptomatic revealed higher levels of HSCRP in their sera. No significant correlation was found between the mean serum levels of HSCRP with symptoms of MDD.

Table 5. Difference in the distribution of WBCs count in terms the severity of depressive thoughts

Variable	Severity of Depression	Mean±SD	P
WBCs count	Mild	7.740±1.8746	0.12
	Moderate- severe	8.565±2.4142	

WBC: white blood cell.

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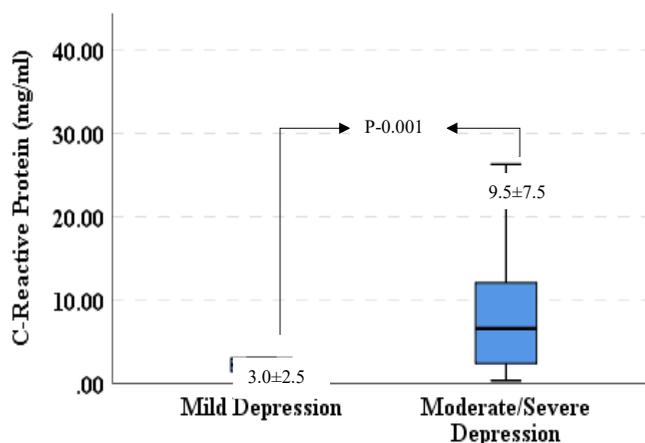


Figure 1. Boxplot distribution of HSCRP in terms of depression severity based on PHQ-9 scores
 HSCRP: high sensitive C-reactive protein; PHQ-9: the 9-item patient health questionnaire.

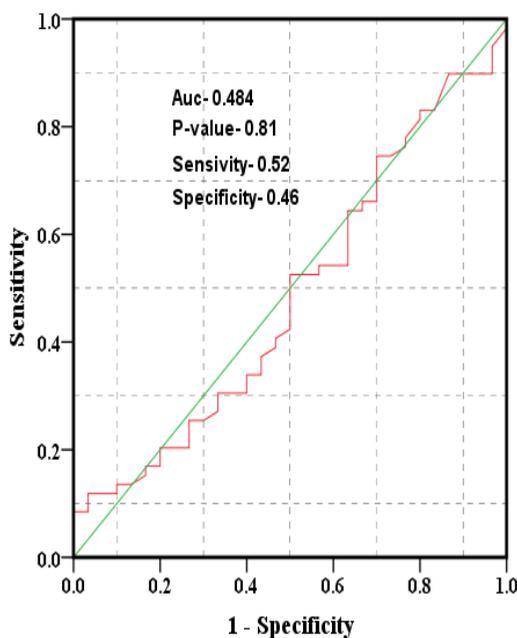


Figure 2. ROC-Curve Diagnostic Ability of HSCRP to Distinguish Those With Severe MDD From Those With no or Mild Depressive Thoughts

HSCRP: high sensitive C-reactive protein; MDD: major depressive disorder; ROC-curve: receiver operating characteristic curve.

Ethical Considerations

Compliance with ethical guidelines

This study and its protocol were approved by the authority of the health institution at Merjan Teaching Hospital (Code: MH., EC: 12-8-2020, 110772). Also, we applied the American Psychological Association’s ethical principles. The involved applicants (or their relatives) provided

a written informed agreement. The study did not include any clinical therapeutic trial. The whole research was conducted according to the Helsinki Declaration.

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Authors' contributions

Conceptualization: Hayder Abdul-Amir M. Al-Hindy, Amer Fadhil Alhaideri; Methodology: Amer Fadhil Alhaideri, Azher Nema Mohammed Al-Agam; Investigation: Ammar Waheeb Obeiad; Writing – original draft: Hayder Abdul-Amir M. Al-Hindy, Mahir Abdulkadhum Khudhair Alzughaihi; Writing – review & editing: All authors; Supervision: Hayder Abdul-Amir M. Al-Hindy.

Conflict of interest

The authors declared no conflict of interest.

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